REMARKS

Applicants would like to thank the Examiner for granting a telephone interview on July 22, 2003, regarding this application. At the Examiner's suggestion, Applicants have filed herewith a request for continued examination.

In the final Office Action ("Office Action"), the Examiner rejected all pending claims on various grounds. In the subsequently issued advisory action, the Examiner maintained her rejections, which were discussed in the above-mentioned interview. A letter outlining issues to be discussed in the interview was sent to the Examiner on July 21, 2003. Applicants have attached hereto a copy of this letter as "Exhibit A."

Addressed below are issues raised during the interview:

Rejection under 35 U.S.C. § 112, first paragraph

The Examiner rejected claims 24-27 for containing new matter. More specifically, she asserted that there was no support in the specification for the recitation "excludes the non-receptor binding domain of the Pseudomonas exotoxin A" in these claims. See the Office Action, page 3, part 11.

In the response to the Office Action, Applicants pointed out that the recitation was supported by a working example of the specification and therefore contained no new matter. Applicants reiterated this position during the interview. The Examiner maintained her rejection, but suggested deleting the recitation from the rejected claims and using the phrase "consisting of." Applicants have amended the claims accordingly and request the rejection be withdrawn.

Rejection under 35 U.S.C. § 102

The Examiner rejected claims 14, 15, 17, and 18 on two grounds, each of which is discussed in detail below:

I

Claims 14 and 18 were rejected as being anticipated by Lorberboum-Galski et al. (U.S. Patent No. 6,140,066, "Lorberboum-Galski"), as evidenced by Burnie et al. (European Application No. 0 406 029 A1). See the Office Action, page 4, part 12.

Claim 14 covers a nucleic acid encoding a polypeptide that contains (1) the receptor binding domain of a Pseudomonas exotoxin A (PE), and (2) at least three copies of an antigenic peptide sequence. It is well known in the art that an antigenic peptide contains at least one epitope. An epitope has a stable spatial conformation so that it can stimulate the immune system to generate specific antibodies that recognize the spatial conformation. Lorberboum-Galski discloses a DNA sequence encoding a polypeptide including the full-length PE and 1 to 3 copies of "flexible" linker sequence of GGGGS. See column 2, lines 56-59. As the linker is flexible, i.e., conformationally unstable, it is not antigenic. Thus, Lorberboum-Galski does not anticipate claim 14.

Applicants presented the above arguments during the interview. However, the Examiner appeared to have misinterpreted "conformationally stable/unstable" as "chemically stable/unstable." Applicants have taken this opportunity to clarify this confusion.

Claim 18 covers a nucleic acid encoding a polypeptide that contains (1) the receptor binding domain of a PE, and at least three continuous copies of an antigenic peptide sequence. For the same reasons set forth above, this claim is also not anticipated by Lorberboum-Galski.

II

The Examiner further rejected claims 14, 15, 17, and 18, contending that they are anticipated by Hickey et al. (WO 97/15325, "Hickey"). See the Office Action, pages 4 and 5, part 13.

Claims 14 and 18 have been discussed in Part I above. Claim 15 is drawn to a nucleic acid similar to that of claim 14 except that the nucleic acid encodes a polypeptide having at least 3 copies of a peptide sequence containing SEQ ID NO:1 (i.e., GnRH). Claim 17 covers a nucleic acid similar to that of claim 14 except that the nucleic acid encodes a polypeptide having 10 to

20 copies of an antigenic peptide sequence. All of the nucleic acids of these four claims include a sequence encoding at least three copies of an antigenic peptide sequence.

It is the Examiner's position that Hickey teaches using recombinant DNA techniques to generate GnRH-PE hybrid proteins. See the Office Action, page 5, lines 10-18. Nonetheless, according to Hickey, there are two tandem repeats of GnRH in such a GnRH-PE hybrid protein (see page 9, lines 29-32). Hickey does not teach using recombinant DNA techniques to generate GnRH-PE hybrid proteins having at least three GnRH. It therefore does not anticipate claims 14, 15, 17, and 18.

Referring to page 13 of Hickey, the Examiner concluded that Hickey teaches an immunogenic system containing 2-20 GnRHs, and therefore anticipated the above-mentioned claims. See the Office Action, page 5, lines 15-17. Formula I at page 13 of Hickey shows a GnRH-scaffold PE conjugate that contains 2-20 GnRHs. Note that each GnRH ("X") branches out from the scaffold. The Hickey immunogenic system therefore is a branched polymer. In contrast, all of claims 14, 15, 17, and 18 are drawn to nucleic acids, which are linear polymers. Indeed, these nucleic acids encode polypeptides, which are also linear polymers. They clearly differ from the GnRH-scaffold PE conjugate of Hickey.

Therefore, Hickey does not anticipate claims 14, 15, 17, and 18.

Rejection under 35 U.S.C. § 103(a)

The Examiner rejected claims 24-27 as being obvious over Hickey in view of Hwang et al. (J. Biol. Chem. 264:2379-2384, 1989) and Pastan et al. (U.S. Patent No. 4,892,827, "Pastan"). See the Office Action, page 5, lines 22-24. Applicants respectfully traverse.

Claims 24-27, as amended, are drawn to nucleic acids encoding a polypeptide that includes (1) a PE fragment containing only the receptor binding domain of a PE, i.e., domain Ia; and (2) at least two copies of an antigenic peptide sequence. In the response to the Office Action, Applicants pointed out that the three cited references would not have motivated one skilled in the art to combine their teachings to make the nucleic acids of the claims at issue. Both Hickey and Pastan teach PE immunogenic carriers excluding domain Ia. Hickey teaches that

"preferred Pseudomonas exotoxin variants are [those] having decreased toxicity ... having amino acids 1-252 (domain Ia) deleted." See, e.g., the paragraph bridging pages 9 and 10. Pastan teaches that "PE molecules with a deletion of Domain Ia are effective immunotoxins with diminished side effects ..." See column 3, lines 15-18. To the extent that these two references point out undesirable side effects of domain Ia, they both teach away including this domain in an immunogenic carrier. Of note, Hwang teaches that domain Ia can be used as an antigen for producing vaccines against PE but not an immunogenic carrier as taught in Hickey. Thus, the 3 references, alone or combined, would not have motivated one skilled in the art to make the nucleic acids of claims 24-27.

During the interview, the Examiner refused to consider Applicants' arguments set forth above, asserting that Pastan encouraged using a PE sequence containing domain Ia. To support her assertion, she relied on a passage in Pastan, i.e., "PE Ia is more than 100 times less toxic on a weight basis than native PE (column 6, lines 27-28)." The Examiner apparently misread "PE Ia" as a PE sequence containing domain Ia. On the contrary, "PE Ia" is a PE sequence lacking domain Ia. See column 6, lines 23-24. Therefore, as the Applicants pointed out, Pastan discourages the using of a PE sequence containing domain Ia.

For the reasons set forth above, Applicants submit that claims 24-27 are non-obvious over the three references cited by the Examiner, and the rejection should be withdrawn.

CONCLUSION

Applicants submit that grounds for the rejections asserted by the Examiner have been overcome, and that claims, as pending, define subject matter that contains no new matter and is novel and non-obvious. On this basis, it is submitted that allowance of this application is proper, and early favorable action is solicited.

Enclosed is a $465.00 check for the Petition for Three-Mont Extension of Time fee. Please apply any other charges to deposit account 06-1050, referencing Attorney Docket No. 08919-022001.

Respectfully submitted,

Date: 9-10-03

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